

Appl. No. : 09/815,242
Filed : March 21, 2001

REMARKS

Applicants have reviewed the rejection of claims 12, 31, 45-69 and 71-102 as set out in the instant Final Office Action. After careful consideration, Applicants respectfully traverse this rejection.

Claim Rejection Based on 35 U.S.C. § 112, first paragraph

Claims 12, 31, 45-69 and 71-102 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner asserts that “the claimed invention encompasses **any gene product** in a cell whose activity is reduced by **an antisense**, thereby producing a sensitized cell.” Additionally, the Examiner notes, that because of polar effects in bacteria, antisense inhibition of a single known essential gene in an operon might result in the inhibition of expression of other downstream genes present in the operon. The Examiner then asserts that the number of genes and gene products disclosed in the specification does not adequately support the elected claims. In particular, it is alleged that the specification does not provide sufficient species to permit a skilled artisan to envision the structure of the antisense nucleic acids which may be used to carry out the claimed method because the structure of such antisense nucleic acids is highly variant.

Applicants respectfully disagree with the Examiner’s construction of the elected claims. The elected claim set comprises two independent claims (claim 12 and 31) as well as claims dependent thereon. Neither of the independent claims (nor the claims dependent thereon) are drawn to an invention that encompasses “**any gene product** in a cell whose activity is reduced by **an antisense**, thereby producing a sensitized cell.” Rather the claims are drawn to providing an antisense nucleic acid to reduce the activity or amount of a gene product whose activity or amount is reduced by an antisense comprising a nucleotide sequence having a specific sequence identification number. For example, Claim 12, which is drawn to a method for screening a candidate compound for the ability to reduce cellular proliferation, includes, in relevant part, the step of providing a sublethal level of an antisense nucleic acid complementary to at least a portion of a nucleic acid encoding a gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell, **wherein said gene product is a**

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gene product whose activity or amount is reduced by an antisense nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 521, 1390, 1463, 2782 and 3283. (Emphasis added). Thus, contrary to the Examiner's assertion, this claim language is not commensurate in scope with "any gene product in a cell whose activity or amount is reduced by an antisense, thereby producing a sensitized cell."

In view of the claim language, Applicants maintain that the exemplary antisense nucleic acids, coding sequences and polypeptide gene products that are described in the specification are sufficient to support the elected claim set. As discussed in the previous response, the specification describes several *yphC* genes from a variety of cells, the gene products encoded by those genes, and antisense nucleic acids that are capable of reducing the activity or amount of such *yphC* gene products. The Examiner contends that antisense nucleic acids, which are capable of reducing the activity or amount of a gene product whose activity or amount is reduced by antisense nucleotide sequence selected from the group consisting of SEQ ID NOs: 521, 1390, 1463, 2782 and 3283, are highly variant, and thus, the representative antisense sequences provided by the Applicants are insufficient to show possession of the claimed methods at the time of the invention. The Applicants respectfully disagree with this contention.

In addition to the specific inhibitory antisense nucleic acids complementary to *yphC* that are described in the instant specification and listed in the accompanying sequence listing, the specification describes many other antisense nucleic acids which are capable of reducing the activity or amount of a gene product whose activity or amount is reduced by antisense nucleotide sequence selected from the group consisting of SEQ ID NOs: 521, 1390, 1463, 2782 and 3283. In particular, the specification describes all possible inhibitory antisense nucleic acids complementary to the *yphC* genes recited in the instant application as well as inhibitory antisense sequences upstream and downstream of the *yphC* gene in the operon in which the *yphC* gene is located. This point is appropriately illustrated by Example number 15 of the Written Description Training Materials (available at the USPTO website) which is based on and in accordance with the Written Description Guidelines (66 FR 1099, January 5, 2001) promulgated by the USPTO. Example 15 of the Training Materials sets out a case where the written description of an application supports a claim to broad genus of antisense molecules that inhibit the production of human growth hormone (HGH). In this example, the applicant has disclosed SEQ ID NO: 1 (HGH) and has stated that the invention includes antisense oligonucleotides complementary to

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SEQ ID NO: 1. The applicant has also described a method of screening for antisense molecules. The example goes on to state that it well known in the art that a full-length antisense nucleic acid has inhibitory activity as do fragments of the full-length antisense nucleic acid provided that they match accessible regions of the target nucleic acid. In consideration of the description provided by the applicant in Example 15, the Training Materials go on to state that, in view of the level of knowledge in the art, a skilled artisan would recognize that the applicant possessed the genus embraced by a claim drawn to all antisense nucleic acids complementary to SEQ ID NO: 1 which inhibit HGH production, because the applicant has disclosed a full-length HGH sequence, a functional characteristic of the antisense nucleic acids (the inhibitory function) and a method of screening for such antisense nucleic acids. Accordingly, the Training Materials state that the claim in Example 15 is adequately described.

Like the applicants in Example 15 of the training materials, the instant Applicants have described the full-length *yphC* coding nucleotide sequences for several cells, including both Gram negative and Gram positive bacteria, as well as the full-length complementary sequences (full-length antisense nucleotide sequences). In addition to the full-length antisense, Applicants have provided several working examples describing particular antisense nucleic acids that are complementary to at least a portion of the *yphC* gene and which can be used to sensitize a cell having a *yphC* gene (e.g. sensitizing the cell by inhibiting cellular proliferation). Applicants have also described a method of screening for additional antisense nucleic acids which have activity against the *yphC* gene and products thereof. In particular, Applicants describe a method for introducing an antisense nucleic acid into a cell and determining the extent of the inhibition of cellular proliferation that results (see Example 1 at page 114, line 11 to page 120, line 13). Applicants further describe the isolation and characterization of antisense nucleic acids that are determined to have proliferation-inhibiting activity (see Examples 1 and 2 at page 114, line 11 to page 123, line 24) and also provide numerous antisense nucleic acids comprising at least, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 consecutive nucleotides of a sequences complementary to the *yphC* gene or complementary to a nucleotide sequence encoding a YphC protein which can be screened for activity against the *yphC* gene and its products using the above method (page 97, line 8 to page 102, line 10). Given the description provided in the specification, one of ordinary skill in the art would appreciate that antisense nucleic acid fragments from any portion of the *yphC* gene can be assayed for the ability to inhibit cellular

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proliferation. In accordance with Example 15 of the Written Description Training Materials, the instant specification adequately describes all possible inhibitory antisense nucleotide sequences complementary to the *yphC* gene.

In addition to having described antisense nucleotide sequences complementary to *yphC* genes, Applicants have also described antisense nucleotide sequences both upstream and downstream from the *yphC* gene that are in the same operon. In particular, Example 4 of the specification states that due to polar effects, the activity or amount of an essential gene product, which is produced by an essential gene that is located on an operon, may be reduced by an antisense nucleic acid that is not complementary to the essential gene, but rather, is complementary to a gene or nucleotide region upstream of the essential gene in the operon (see page 127, lines 1-10). For many different microbes, the nucleotide sequence both upstream and downstream of the *yphC* gene was well known to those of ordinary skill in the art at the time of filing the instant application. In fact, the instant specification directs those of skill in the art to electronic sequence databases comprising the complete genome sequences for numerous organisms (see page 124, lines 6-21; page 125, lines 36-40; and page 127, lines 17-29). For example, the complete genome of *Haemophilus influenzae* has been known since 1995 (Fleischmann, R.D., et al. 1995. *Science* **269**:496-512 – Exhibit A). The sequencing of the *Escherichia coli* genome was completed in 1997 (Blattner, F.R., et al. 1997. *Science* **277**:1432-4 – Exhibit B), and the genome of *Pseudomonas aeruginosa* was finished in 2000 (Stover, C.K., et al. 2000. *Nature* **406**:959-64 – Exhibit C). In total, the entire genome sequence of at least 40 different microbes was known and publicly available prior to the filing date of the instant application (Exhibit D – see also page 124, lines 6-21). In addition to the foregoing, the instant specification directs those of skill in the art to electronic sequence databases comprising nearly complete or partial genome sequences for additional organisms (see page 124, lines 5-12; page 125, line 40 to page 126, line 3; and page 127, line 30 to page 128, line 4). For example, the genome of *Staphylococcus aureus* was nearly complete at the time of filing the instant application. The complete genome of *S. aureus* was made publicly available on April 21, 2001 (Kuroda, M., et al. 2001. *Lancet* **357**:1218-9 – Exhibit E). Furthermore, at the time of filing, nearly complete genome sequences of many other microbial species were available (see Examples 3 and 4 page 123, line 25 to page 129, line 3). Given the public availability of microbial genomes at the time of filing the instant application and the teachings of the

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specification, one or ordinary skill in the art would readily appreciate that Applicants demonstrated possession of the full-length coding and antisense sequence of the entire *yphC* operon. Using the same reasoning as described above and presented in Example number 15 of the Written Description Training Materials, a skilled artisan would also appreciate that Applicants have described the all the possible inhibitory antisense sequences that are complementary to at least a portion of the *yphC* operon by describing the full-length antisense sequence complementary to the operon, the function of this sequence and fragments thereof, and a method for determining whether the antisense fragments have the stated inhibitory activity. Accordingly, at the time of filing the instant application, a skilled artisan would have concluded that Applicants possessed the antisense sequences recited in the claimed methods.

In view of the above arguments, Applicants submit that the instant specification provides adequate written description for each of the elected claims (Claims 12, 31, 45-69 and 71-102). Accordingly, Applicants respectfully request that the Examiner withdraw her rejection of Claims 12, 31, 45-69 and 71-102 under 35 U.S.C. § 112, first paragraph.

CONCLUSION


Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

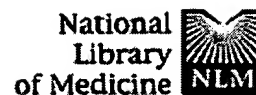
Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 22, 2004

By: 
Jerry L. Hefner
Registration No. 53,009
Attorney of Record
Customer No. 20,995
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- Science. 1995 Jul 28;269(5223):468-70.
- Science. 1995 Sep 29;269(5232):1805.
- Science. 1996 Mar 1;271(5253):1302-3; author reply 1303-4.
- Science. 1996 Mar 1;271(5253):1302; author reply 1303-4.

Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd.**Fleischmann RD, Adams MD, White O, Clayton RA, Kirkness EF, Kerl AR, Bult CJ, Tomb JF, Dougherty BA, Merrick JM, et al.**

Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

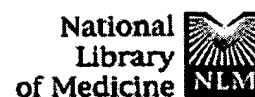
An approach for genome analysis based on sequencing and assembly of unsequenced pieces of DNA from the whole chromosome has been applied to obtain the complete nucleotide sequence (1,830,137 base pairs) of the genome from the bacterium *Haemophilus influenzae* Rd. This approach eliminates the need for initial mapping efforts and is therefore applicable to the vast array of microbial species for which genome maps are unavailable. The *H. influenzae* Rd genome sequence (Genome Sequence DataBase accession number L42023) represents only complete genome sequence from a free-living organism.

PMID: 7542800 [PubMed - indexed for MEDLINE]

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Exhibit A



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- Science. 1997 Sep 5;277(5331):1432-4.
- Science. 1998 Mar 20;279(5368):1827.

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The complete genome sequence of Escherichia coli K-12.

Blattner FR, Plunkett G 3rd, Bloch CA, Perna NT, Burland V, Riley M, Collado-Vides J, Glasner JD, Rode CK, Mayhew GF, Gregor J, Davis N, Kirkpatrick HA, Goeden MA, Rose DJ, Mau B, Shao Y.

Laboratory of Genetics, University of Wisconsin-Madison, 445 Henry Mall, Madison, WI 53706, USA. ecoli@genetics.wisc.edu

The 4,639,221-base pair sequence of Escherichia coli K-12 is presented. Of 4 protein-coding genes annotated, 38 percent have no attributed function. Comparison with five other sequenced microbes reveals ubiquitous as well as narrowly distributed gene families; many families of similar genes within E. coli are also evident. The largest family of paralogous proteins contains 80 ABC transporters. The genome as a whole is strikingly organized with respect to local direction of replication; guanines, oligonucleotides possibly related to replication and recombination, and most genes are so oriented. The genome also contains insertion sequence (IS) elements, phage remnants, and many other patches of unusual composition indicating genome plasticity through horizontal transfer.

PMID: 9278503 [PubMed - indexed for MEDLINE]

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Exhibit B



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Comment in:

- Nature. 2000 Aug 31;406(6799):947-8.

nature

Complete genome sequence of *Pseudomonas aeruginosa* PA01, a opportunistic pathogen.

Stover CK, Pham XQ, Erwin AL, Mizoguchi SD, Warrenner P, Hickey M, Brinkman FS, Hufnagle WO, Kowalik DJ, Lagrou M, Garber RL, Goltr Tolentino E, Westbrook-Wadman S, Yuan Y, Brody LL, Coulter SN, Fo KR, Kas A, Larbig K, Lim R, Smith K, Spencer D, Wong GK, Wu Z, Pa IT, Reizer J, Saier MH, Hancock RE, Lory S, Olson MV.

PathoGenesis Corporation, Seattle, Washington 98119, USA.

Pseudomonas aeruginosa is a ubiquitous environmental bacterium that is one the top three causes of opportunistic human infections. A major factor in its prominence as a pathogen is its intrinsic resistance to antibiotics and disinfectants. Here we report the complete sequence of *P. aeruginosa* strain PA01. At 6.3 million base pairs, this is the largest bacterial genome sequenced, and the sequence provides insights into the basis of the versatility and intrinsic drug resistance of *P. aeruginosa*. Consistent with its larger genome size and environmental adaptability, *P. aeruginosa* contains the highest proportion of regulatory genes observed for a bacterial genome and a large number of genes involved in the catabolism, transport and efflux of organic compounds as well as four potential chemotaxis systems. We propose that the size and complexity of the *P. aeruginosa* genome reflect an evolutionary adaptation permitting it to thrive in diverse environments and resist the effects of a variety of antimicrobial substances.

PMID: 10984043 [PubMed - indexed for MEDLINE]

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Exhibit C

COMPLETE MICROBIAL GENOMES

**BLAST2 on Complete genomes at INFOBIOGEN**

(Select BLASTN or TBLASTN and "Genomes Complets")

FASTA on Complete genomes at INFOBIOGEN

(Select FASTA or TFASTA or TFASTX and "Genomes Complets")

Updated, April 6, 2004

		Genome Taxonomy NCBI	Size (Mb)	Base pairs	Date	SRS Accession	Séquences (FASTA) (*)	ID
1	<input checked="" type="checkbox"/>	<u>Mycoplasma genitalium</u>	0.58	580,073	Jan 23, 1998	<u>L43967</u>	<u>mgen.seq</u>	<u>mgen.mne</u>
2	<input checked="" type="checkbox"/>	<u>Haemophilus influenzae</u>	1.83	1,830,135	Jan 23, 1998	<u>L42023</u>	<u>hin.seq</u>	<u>hin.mne</u>
3	<input checked="" type="checkbox"/>	<u>Methanococcus jannaschii</u>	1.66	1,664,970	May 30, 1998	<u>L77117</u>	<u>mjan.seq</u>	<u>mjan.mne</u>
4	<input checked="" type="checkbox"/>	<u>Synechocystis sp</u>	3.57	3,573,470	Jan 23, 1998	<u>AB001339</u>	<u>gsyn.seq</u>	<u>gsyn.mne</u>
5	<input checked="" type="checkbox"/>	<u>Mycoplasma pneumoniae M129</u>	0.81	816,444	Jan 23, 1998	<u>U00089</u>	<u>mpne.seq</u>	<u>mpne.mne</u>
6	<input checked="" type="checkbox"/>	<u>Escherichia coli</u>	4.63	4,638,858	Jan 23, 1998	<u>U00096</u>	<u>ecoli.seq</u>	<u>ecoli.mne</u>
7	<input checked="" type="checkbox"/>	<u>Helicobacter pylori strain 26695</u>	1.66	1,667,867	Jun 2, 1998	<u>AE000511</u>	<u>hpyl.seq</u>	<u>hpyl.mne</u>
8	<input checked="" type="checkbox"/>	<u>Archaeoglobus fulgidus</u>	2.17	2,178,400	Jan 23, 1998	<u>AE000782</u>	<u>aful.seq</u>	<u>aful.mne</u>
9	<input checked="" type="checkbox"/>	<u>Methanobacterium thermoautotrophicum</u>	1.75	1,751,377	Jan 23, 1998	<u>AE000666</u>	<u>mthe.seq</u>	<u>mthe.mne</u>
10	<input checked="" type="checkbox"/>	<u>Bacillus subtilis</u>	4.21	4,214,814	Jan 23, 1998	<u>AL009126</u>	<u>bsub.seq</u>	<u>bsub.mne</u>
11	<input checked="" type="checkbox"/>	<u>Borrelia burgdorferi</u>	0.91	914,726	Apr 16, 1998	<u>AE000783</u>	<u>bbur.seq</u>	<u>bbur.mne</u>
12	<input checked="" type="checkbox"/>	<u>Aquifex aeolicus</u>	1.59	1,595,349	May 30, 1998	<u>AE000657</u>	<u>aaeo.seq</u>	<u>aaeo.mne</u>
13	<input checked="" type="checkbox"/>	<u>Pyrococcus horikoshii</u>	1.73	1,738,505	May 30, 1998	<u>AP000001</u>	<u>phor.seq</u>	<u>phor.mne</u>
14	<input checked="" type="checkbox"/>	<u>Mycobacterium</u>	4.42	4,420,017	Jun 29,	<u>AL123456</u>	<u>mt.seq</u>	<u>mt.mne</u>

Exhibit D

		tuberculosis H37Rv			1998			
15	■	<u>Treponema pallidum</u>	1.14	1,143,171	Jul 18, 1998	<u>AE000520</u>	<u>tpal.seq</u>	<u>tpal.mne</u>
16	■	<u>Chlamydia trachomatis</u>	1.04	1,047,739	Sep 2, 1998	<u>AE001273</u>	<u>ctra.seq</u>	<u>ctra.mne</u>
17	■	<u>Rickettsia prowazekii</u>	1.11	1,110,773	Nov 15, 1998	<u>AJ235269</u>	<u>rpro.seq</u>	<u>rpro.mne</u>
18	■	<u>Helicobacter pylori</u> <u>strain J99</u>	1.64	1,643,831	Jan 17, 1999	<u>AE001439</u>	<u>hpyl2.seq</u>	<u>hpyl2.mne</u>
19	■	<u>Chlamydia pneumonia</u>	1.23	1,236,350	Mar 16, 1999	<u>AE001363</u>	<u>cpne.seq</u>	<u>cpne.mne</u>
20	■	<u>Pyrococcus abyssi</u>	1.76	1,765,118	July, 1999	<u>AL096836</u>	<u>paby.seq</u>	<u>paby.mne</u>
21	■	<u>Thermotoga maritima</u>	1.8	1,860,725	June 2, 1999	<u>AE000512</u>	<u>tmar.seq</u>	<u>tmar.mne</u>
22	■	<u>Aeropyrum pernix</u>	1.7	1,669,695	June 24, 1999	<u>AP000058</u>	<u>aper.seq</u>	<u>aper.mne</u>
23	■	<u>Deinococcus</u> <u>radiodurans R1</u>	3.0	3,074,955	November 24, 1999	<u>AE001825</u>	<u>drad.seq</u>	<u>drad.mne</u>
24	■	<u>Ureaplasma urealyticum</u>	0.8	755,199	February 7, 2000	<u>AE002100</u>	<u>uure.seq</u>	<u>uure.mne</u>
25	■	<u>Campylobacter jejuni</u> <u>NCTC11168</u>	1.7	1,641,481	Feb 14, 2000	<u>CJ11168X1</u>	<u>cjej.seq</u>	<u>cjej.mne</u>
26	■	<u>Chlamydia muridarum</u>	1.08	1,082,508	Mar 10, 2000	<u>AE002269</u>	<u>cmur.seq</u>	<u>cmur.mne</u>
27	■	<u>Chlamydophila</u> <u>pneumoniae AR39</u>	1.24	1,236,093	Mar 10, 2000	<u>AE002164</u>	<u>cppn.seq</u>	<u>cppn.mne</u>
28	■	<u>Neisseria meningitidis</u> <u>MC58</u>	2.3	2,284,651	Mar 13, 2000	<u>AE002098</u>	<u>nmen.seq</u>	<u>nmen.mne</u>
29	■	<u>Neisseria meningitidis</u> <u>Z2491</u>	2.3	2,184,918	Apr 6, 2000	<u>AL162752</u>	<u>nm.seq</u>	<u>nm.mne</u>
30	■	<u>Xylella fastidiosa</u>	2.7	2,729,130	July 15, 2000	<u>AE003850</u>	<u>xfas.seq</u>	<u>xfas.mne</u>
31	■	<u>Vibrio cholerae N16961</u> <u>El Tor</u>	4.0	4,057,596	Aug 5, 2000	<u>AE003852</u>	<u>vcho.seq</u>	<u>vcho.mne</u>
32	■	<u>Pseudomonas</u> <u>aeruginosa PAO1</u>	6.2	6,,264,403	Sep 7, 2000	<u>AE004091</u>	<u>paer.seq</u>	<u>paer.mne</u>
33	■	<u>Bacillus halodurans C-</u> <u>125</u>	4.2	4,203,003	Sep 17, 2000	<u>BA000004</u>	<u>bhal.seq</u>	<u>bhal.mne</u>
34	■	<u>Halobacterium sp.</u> <u>NRC-1</u>	2.0	2,024,379	Oct 6, 2000	<u>AE004437</u>	<u>hals.seq</u>	<u>hals.mne</u>
		<u>Thermoplasma</u>			Oct 6,			

Exhibit D

35	■	<u>acidophilum</u>	1.56	1,565,106	2000	<u>AL139299</u>	<u>taci.seq</u>	<u>taci.mne</u>
36	■	<u>Chlamydomphila pneumoniae</u> CWL029	1.2	1,200 000	Dec 11, 2000	<u>AE001586</u>	<u>cphp.seq</u>	<u>cphp.mne</u>
37	■	<u>Chlamydomphila pneumoniae</u> J138	1.2	1,200 000	Dec 11, 2000	<u>AP002545</u>	<u>cppo.seq</u>	<u>cppo.mne</u>
38	■	<u>Thermoplasma volcanium</u> GSS1	1.6	1,585,104	Dec 25, 2000	<u>AP000991</u>	<u>tvol.seq</u>	<u>tvol.mne</u>
39	■	<u>Mesorhizobium loti</u>	7.3	7,036,071	Jan 2, 2001	<u>AP002994</u>	<u>mlot.seq</u>	<u>mlot.mne</u>
40	■	<u>Escherichia coli</u> O157:H7	5.5	5,500,666	Jan 27, 2001	<u>AE005174</u>	<u>ecoo.seq</u>	<u>ecoo.mne</u>
41	■	<u>Pasteurella multocida</u> PM70	2.2 ?	2,269,587	Feb 7, 2001	<u>AE006034</u>	<u>pmul.seq</u>	<u>pmul.mne</u>
42	■	<u>Lactococcus lactis</u> subsp. <u>lactis</u> IL1403	2.3	2,378,519	Feb 12, 2001	<u>AE006239</u>	<u>llac.seq</u>	<u>llac.mne</u>
43	■	<u>Mycobacterium leprae</u>	2.8	3,268,203	Feb 23, 2001	<u>AL450380</u>	<u>mlep.seq</u>	<u>mlep.mne</u>
44	■	<u>Escherichia coli</u> O157:H7 sub RIMD 0509952	5.5	5,499,400	Mar 22, 2001	<u>BA000007</u>	<u>ecop.seq</u>	<u>ecop.mne</u>
45	■	<u>Caulobacter crescentus</u>	4	4,038,387	Mar 23, 2001	<u>AE005673</u>	<u>ccre.seq</u>	<u>ccre.mne</u>
46	■	<u>Streptococcus pyogenes</u> strain SF370 serotype M1	1,8	1,852,442	Apr 17, 2001	<u>AE004092</u>	<u>spyo.seq</u>	<u>spyo.mne</u>
47	■	<u>Staphylococcus aureus</u> (strain:N315)	2,8	2,838,744	Apr 23, 2001	<u>BA000018</u>	<u>saun.seq</u>	<u>saun.mne</u>
48	■	<u>Staphylococcus aureus</u> (strain:Mu50)	2,8	2,878,484	Apr 30, 2001	<u>BA000017</u>	<u>sauo.seq</u>	<u>sauo.mne</u>
49	■	<u>Sulfolobus solfataricus</u>	3.0	3,008,365	Apr 30, 2001	<u>AE006641</u>	<u>ssol.seq</u>	<u>ssol.mne</u>
50	■	<u>Mycobacterium tuberculosis</u> CDC1551	4,4	4,420,576	May 2, 2001	<u>AE000516</u>	<u>mtuc.seq</u>	<u>mtuc.mne</u>
51	■	<u>Mycoplasma pulmonis</u> (strain UAB CTIP)	0.93	963,979	May 17, 2001	<u>AL445566</u>	<u>mpul.seq</u>	<u>mpul.mne</u>
52	■	<u>Sinorhizobium meliloti</u> plasmid pSymA	1.3	1,361,426	Jul 14, 2001	<u>AE007195</u>	<u>smel.seq</u>	<u>smel.mne</u>
53	■	<u>Clostridium acetobutylicum</u> ATCC824	4.5	4,155,410	Jul 30, 2001	<u>AE001437</u>	<u>cace.seq</u>	<u>cace.mne</u>
54	■	<u>Sinorhizobium meliloti</u> chromosome	3.6	3,654,685	Aug 3, 2001	<u>AL591688</u>	<u>smec.seq</u>	<u>smec.mne</u>

Exhibit D







55		<u>Agrobacterium tumefaciens strain C58 circular chromosome</u>	2.8	2,856,721	Aug 21, 2001	<u>AE007869</u>	<u>atum.seq</u>	<u>atum.mne</u>
56		<u>Streptococcus pneumoniae TIGR4</u>	2.2	2,172,327	Sep 2, 2001	<u>AE005672</u>	<u>spne.seq</u>	<u>spne.mne</u>
57		<u>Streptococcus pneumoniae R6</u>	2.0	2,049,595	Sep 9, 2001	<u>AE007317</u>	<u>spnf.seq</u>	<u>spnf.mne</u>
58		<u>Sulfolobus tokodaii</u>	2.6	2,695,206	Sep 19, 2001	<u>BA000023</u>	<u>stok.seq</u>	<u>stok.mne</u>
59		<u>Rickettsia conorii Malish 7</u>	1.3	1,275,535	Sep 19, 2001	<u>AE006914</u>	<u>rcon.seq</u>	<u>rcon.mne</u>
60		<u>Agrobacterium tumefaciens strain C58 linear chromosome</u>	2.0	2,085,892	Sep 21, 2001	<u>AE007870</u>	<u>atul.seq</u>	<u>atul.mne</u>
61		<u>Yersinia pestis strain CO92</u>	4.6	4,654,678	Oct 6, 2001	<u>AL590842</u>	<u>ypes.seq</u>	<u>ypes.mne</u>
62		<u>Listeria innocua Clip11262</u>	3.0	3,011,758	Oct 27, 2001	<u>AL592022</u>	<u>linn.seq</u>	<u>linn.mne</u>
63		<u>Listeria monocytogenes strain EGD</u>	2.9	2,945,078	Oct 27, 2001	<u>AL591824</u>	<u>lmon.seq</u>	<u>lmon.mne</u>
64		<u>Salmonella typhimurium LT2</u>	4.8	4,870,812	Oct 28, 2001	<u>AE006468</u>	<u>sthy.seq</u>	<u>sthy.mne</u>
65		<u>Salmonella enterica serovar Typhi</u>	4.8	4,809,987	Oct 28, 2001	<u>AL513382</u>	<u>sthi.seq</u>	<u>sthi.mne</u>
66		<u>Nostoc sp PCC 7120</u>	6.4	6,414,671	Nov 30, 2001	<u>BA000020</u>	<u>nost.seq</u>	<u>nost.mne</u>
67		<u>Brucella melitensis strain 16M chromosomes I and II</u>	3.3	3,312,931	Dec 29, 2001	<u>AE008917</u> <u>AE008918</u>	<u>bmel.seq</u>	<u>bmel.mne</u>
68		<u>Clostridium perfringens</u>	3.0	3,031,880	Jan 16, 2002	<u>BA000016</u>	<u>cper.seq</u>	<u>cper.mne</u>
69		<u>Pyrobaculum aerophilum strain IM2</u>	2.2	2,234,390	Jan 18, 2002	<u>AE009441</u>	<u>pyra.seq</u>	<u>pyra.mne</u>
70		<u>Ralstonia solanacearum GMI1000</u>	5.8	5,812,322	Feb 01, 2002	<u>AL646052</u> <u>AL646053</u>	<u>rsol.seq</u>	<u>rsol.mne</u>
71		<u>Pyrococcus furiosus DSM 3638</u>	1.9	1,918,246	Feb 27, 2002	<u>AE009950</u>	<u>pfur.seq</u>	<u>pfur.mne</u>
72		<u>Wigglesworthia brevipalpis</u>	0.7	697,721	Mar 4, 2002	<u>BA000021</u>	<u>wbre.seq</u>	<u>wbre.mne</u>
73		<u>Fusobacterium nucleatum subsp. nucleatum ATCC 25586</u>	2.1	2,186,280	Mar 27, 2002	<u>AE009951</u>	<u>fnum.seq</u>	<u>fnum.mne</u>

Exhibit D

74	■	<u>Streptococcus pyogenes</u> strain MGAS8232	1,9	1,905,297	Mar 29, 2002	<u>AE009949</u>	<u>spyg.seq</u>	<u>spyg.mne</u>
75	■	<u>Methanopyrus kandleri</u> AV19	1.7	1,703,889	Apr 4, 2002	<u>AE009439</u>	<u>mkan.seq</u>	<u>mkan.mne</u>
76	■	<u>Methanosarcina</u> <u>acetivorans</u> str. C2A	5.7	5,783,472	Apr 5, 2002	<u>AE010299</u>	<u>mace.seq</u>	<u>mace.mne</u>
77	■	<u>Thermoanaerobacter</u> <u>tengcongensis</u> strain MB4T	2.7	2,703,405	May 9, 2002	<u>AE008691</u>	<u>tten.seq</u>	<u>tten.mne</u>
78	■	<u>Streptomyces coelicolor</u>	8.0	8,707,150	May 9, 2002	<u>AL645882</u>	<u>scoe.seq</u>	<u>scoe.mne</u>
79	■	<u>Methanosarcina mazei</u> strain Goe1	4.1	4,119,025	May 21, 2002	<u>AE008384</u>	<u>mmaz.seq</u>	<u>mmaz.mne</u>
80	■	<u>Xanthomonas</u> <u>campestris</u> pv. str. ATCC 33913	5.1	5,103,728	May 29, 2002	<u>AE008922</u>	<u>xcam.seq</u>	<u>xcam.mne</u>
81	■	<u>Xanthomonas</u> <u>axonopodis</u> pv. citri str. 306	5.2	5,203,494	May 29, 2002	<u>AE008923</u>	<u>xaxo.seq</u>	<u>xaxo.mne</u>
82	■	<u>Staphylococcus aureus</u> (strain:MW2)	2,8	2,841,566	May 30, 2002	<u>BA000033</u>	<u>sauw.seq</u>	<u>sauw.mne</u>
83	■	<u>Corynebacterium</u> <u>glutamicum</u> ATCC 13032	3.3	3,309,851	June 6, 2002	<u>BA000036</u>	<u>cglu.seq</u>	<u>cglu.mne</u>
84	■	<u>Buchnera aphidicola</u> str.	0.6	644,814	July 3, 2002	<u>AE013218</u>	<u>baph.seq</u>	<u>baph.mne</u>
85	■	<u>Chlorobium tepidum</u> TLS	2.1	2,166,446	July 4, 2002	<u>AE006470</u>	<u>ctet.seq</u>	<u>ctet.mne</u>
86	■	<u>Streptococcus pyogenes</u> strain MGAS315	1,9	1,902,681	Jul 20, 2002	<u>AE014074</u>	<u>spyq.seq</u>	<u>spyq.mne</u>
87	■	<u>Yersinia pestis</u> strain KIM	4.6	4,625,545	Jul 29, 2002	<u>AE009952</u>	<u>ypet.seq</u>	<u>ypet.mne</u>
88	■	<u>Thermosynechococcus</u> <u>elongatus</u> BP-1	2.5	2,594,257	Aug 31, 2002	<u>BA000039</u>	<u>telo.seq</u>	<u>telo.mne</u>
89	■	<u>Oceanobacillus</u> <u>iheyensis</u>	3,5	3,631,128	Sep 14, 2002	<u>BA000028</u>	<u>oihe.seq</u>	<u>oihe.mne</u>
90	■	<u>Streptococcus agalactiae</u> NEM316	1,3	1,313,350	Sep 19, 2002	<u>AL732656</u>	<u>saga.seq</u>	<u>saga.mne</u>
91	■	<u>Streptococcus agalactiae</u> serotype V	2,1	2,166,207	Sep 19, 2002	<u>AE009948</u>	<u>sagv.seq</u>	<u>sagv.mne</u>
92	■	<u>Bifidobacterium longum</u> NCC2705	2.2	2,268,766	Sep 27, 2002	<u>AE014295</u>	<u>blon.seq</u>	<u>blon.mne</u>

Exhibit D





















93		<u>Brucella suis</u> 1330 chr II	1.2	1,213,801	Oct 4, 2002	<u>AE014292</u>	<u>bsui.seq</u>	<u>bsui.mne</u>
94		<u>Corynebacterium efficiens</u> YS-314	3.1	3,147,590	Oct 5, 2002	<u>BA000035</u>	<u>ceff.seq</u>	<u>ceff.mne</u>
95		<u>Shigella flexneri</u> 2a str. 301	4.6	4,631,693	Oct 18, 2002	<u>AE005674</u>	<u>sfle.seq</u>	<u>sfle.mne</u>
96		<u>Streptococcus mutans</u> UA159	2.0	2,031,491	Oct 28, 2002	<u>AE014133</u>	<u>smut.seq</u>	<u>smut.mne</u>
97		<u>Shewanella oneidensis</u> MR-1	5.0	4,996,813	Dec 05, 2002	<u>AE014299</u>	<u>sone.seq</u>	<u>sone.mne</u>
98		<u>Pseudomonas putida</u> KT2440	6.1	6,183,063	Dec 16, 2002	<u>AE015451</u>	<u>pput.seq</u>	<u>pput.mne</u>
99		<u>Mycoplasma penetrans</u>	1.4	1,358,833	Dec 16, 2002	<u>BA000026</u>	<u>mpen.seq</u>	<u>mpen.mne</u>
100		<u>Vibrio vulnificus</u> CMCP6	5.2	5,127,698	Dec 26, 2002	<u>AE016795</u> <u>AE016796</u>	<u>vvul.seq</u>	<u>vvul.mne</u>
101		<u>Bradyrhizobium japonicum</u>	9.1	9,107,328	Dec 26, 2002	<u>BA000040</u>	<u>bjap.seq</u>	<u>bjap.mne</u>
102		<u>Escherichia coli</u> CFT073	5.2	5,232,448	Dec 26, 2002	<u>AE014075</u>	<u>ecoq.seq</u>	<u>ecoq.mne</u>
103		<u>Staphylococcus epidermidis</u> ATCC 12228	2.5	2,499,759	Jan 3, 2003	<u>AE015929</u>	<u>sepi.seq</u>	<u>sepi.mne</u>
104		<u>Clostridium tetani</u> E88	2.8	2,799,791	Feb 8, 2003	<u>AE015927</u>	<u>cttn.seq</u>	<u>cttn.mne</u>
105		<u>Lactobacillus plantarum</u> strain WCFS1	3.3	3,308,774	Feb 9, 2003	<u>AL935263</u>	<u>lpla.seq</u>	<u>lpla.mne</u>
106		<u>Xylella fastidiosa</u> Temecula1	2.5	2,520,282	Feb 9, 2003	<u>AE015929</u>	<u>xfat.seq</u>	<u>xfat.mne</u>
107		<u>Tropheryma whipplei</u> TW08/27	0.9	926,038	Feb 19, 2003	<u>BX072543</u>	<u>twhi.seq</u>	<u>twhi.mne</u>
108		<u>Vibrio parahaemolyticus</u>	5.1	5,166,520	Mar 7, 2003	<u>BA000031</u> <u>BA000032</u>	<u>vpar.seq</u>	<u>vpar.mne</u>
109		<u>Coxiella burnetii</u> strain RSA 493	1.9	1,995,635	Apr 6, 2003	<u>AE016828</u>	<u>cbur.seq</u>	<u>cbur.mne</u>
110		<u>Streptomyces avermitilis</u>	9.0	9,027,058	Apr 9, 2003	<u>BA000030</u>	<u>save.seq</u>	<u>save.mne</u>
111		<u>Chlamydomophila caviae</u> GPIC	1.1	1,173,570	Apr 16, 2003	<u>AE015925</u>	<u>ccav.seq</u>	<u>ccav.mne</u>
112		<u>Bacillus subtilis</u>	5.4	5,412,829	Apr 17, 2003	<u>AE016877</u>	<u>bcer.seq</u>	<u>bcer.mne</u>

Exhibit D

113	■	<u>Leptospira interrogans</u> serovar lai str. 56601	4.3	4,355,921	Apr 30, 2003	<u>AE010300</u>	<u>lint.seq</u>	<u>lint.mne</u>
114	■	<u>Nitrosomonas europaea</u> ATCC 19718	2.8	2,812,544	May 5, 2003	<u>AL954747</u>	<u>neur.seq</u>	<u>neur.mne</u>
115	■	<u>Bacillus anthracis</u> str. Ames	5.2	5,228,313	May 5, 2003	<u>AE016879</u>	<u>bant.seq</u>	<u>bant.mne</u>
116	■	<u>Mycoplasma</u> <u>gallisepticum</u> strain R	0.9	996,602	June, 11, 2003	<u>AE015450</u>	<u>mgal.seq</u>	<u>mgal.mne</u>
117	■	<u>Mycobacterium bovis</u> AF2122/97	4.3	4,346,142	June, 13, 2003	<u>BX248333</u>	<u>mbov.seq</u>	<u>mbov.mne</u>
118	■	<u>Helicobacter hepaticus</u> ATCC 51449	1.8	1,799,446	Jun 28, 2003	<u>AE017125</u>	<u>hhep.seq</u>	<u>hhep.mne</u>
119	■	<u>Pirellula</u> sp. strain 1	7.1	7,146,726	Jun 30, 2003	<u>BX119912</u>	<u>pisp.seq</u>	<u>pisp.mne</u>
120	■	<u>Haemophilus ducreyi</u> 35000HP	1.6	1,699,255	Aug 4, 2003	<u>AE017143</u>	<u>hduc.seq</u>	<u>hduc.mne</u>
121	■	<u>Chlamydomydia</u> <u>pneumoniae</u> TW-183	11.2	1,226,115	Aug 4, 2003	<u>AE009440</u>	<u>cpnt.seq</u>	<u>cpnt.mne</u>
122	■	<u>Prochlorococcus</u> <u>marinus</u> subsp. <u>marinus</u> str. CCMP1375	1.7	1,751,380	Aug 4, 2003	<u>AE017126</u>	<u>pmas.seq</u>	<u>pmas.mne</u>
123	■	<u>Prochlorococcus</u> <u>marinus</u> MED4	1.6	1,658,190	Aug 19, 2003	<u>BX548174</u>	<u>pmar.seq</u>	<u>pmar.mne</u>
124	■	<u>Prochlorococcus</u> <u>marinus</u> MIT9313	2.4	2,411,173	Aug 19, 2003	<u>BX548175</u>	<u>pmat.seq</u>	<u>pmat.mne</u>
125	■	<u>Tropheryma whipplei</u> str. Twist	0.9	927,423	Aug 19, 2003	<u>AE014184</u>	<u>twht.seq</u>	<u>twht.mne</u>
126	■	<u>Synechococcus</u> sp. WH8102	2.4	2,434,728	Aug 19, 2003	<u>BX548020</u>	<u>syns.seq</u>	<u>syns.mne</u>
128	■	<u>Bordetella pertussis</u> strain Tohama I	4.1	4,086,739	Aug 19, 2003	<u>BX640420</u>	<u>bper.seq</u>	<u>bper.mne</u>
129	■	<u>Bordetella</u> <u>bronchiseptica</u> strain RB50	5.3	5,339,929	Aug 19, 2003	<u>BX470250</u>	<u>bbro.seq</u>	<u>bbro.mne</u>
130	■	<u>Bordetella parapertussis</u> strain 12822	4.8	4,774,201	Aug 19, 2003	<u>BX470249</u>	<u>bpar.seq</u>	<u>bpar.mne</u>
131	■	<u>Chromobacterium</u> <u>violaceum</u> ATCC 12472	4.7	4,751,980	Aug 31, 2003	<u>AE016825</u>	<u>cvio.seq</u>	<u>cvio.mne</u>
132	■	<u>Porphyromonas</u> <u>gingivalis</u> W83	2.3	2,343,896	Sep 4, 2003	<u>AE015924</u>	<u>pgiv.seq</u>	<u>pgiv.mne</u>
133	■	<u>Pseudomonas syringae</u> pv. tomato str. DC3000	6.4	6,398,326	Sep 5, 2003	<u>AE016853</u>	<u>psyn.seq</u>	<u>psyn.mne</u>

134	<input checked="" type="checkbox"/>	<u>Wolinella succinogenes</u>	2.1	2,110,655	Sep 8, 2003	<u>BX571656</u>	<u>wsuc.seq</u>	<u>wsuc.mne</u>
135	<input checked="" type="checkbox"/>	<u>Gloeobacter violaceus</u> <u>PCC 7421</u>	4.6	4,659,769	Sep 28, 2003	<u>BA000045</u>	<u>gvio.seq</u>	<u>gvio.mne</u>
136	<input checked="" type="checkbox"/>	<u>Photorhabdus</u> <u>luminescens subsp.</u> <u>laumondii TTO1</u>	5.6	5,689,787	Sep 30, 2003	<u>BX470251</u>	<u>plum.seq</u>	<u>plum.mne</u>
137	<input checked="" type="checkbox"/>	<u>Geobacter</u> <u>sulfurreducens PCA</u>	4.4	4,426,126	Dec 30, 2003	<u>AE017180</u>	<u>gsul.seq</u>	<u>gsul.mne</u>
138	<input checked="" type="checkbox"/>	<u>Nanoarchaeum equitans</u> <u>Kin4-M</u>	0.5	490,885	Dec 30, 2003	<u>AE017199</u>	<u>nequ.seq</u>	<u>nequ.mne</u>
139	<input checked="" type="checkbox"/>	<u>Bdellovibrio</u> <u>bacteriovorus</u>	3.7	3,783,450	Feb 5, 2004	<u>BX842601</u>	<u>bbac.seq</u>	<u>bbac.mne</u>
140	<input checked="" type="checkbox"/>	<u>Lactobacillus johnsonii</u> <u>NCC 533</u>	1.9	1,993,036	Feb 5, 2004	<u>AE017198</u>	<u>ljoh.seq</u>	<u>ljoh.mne</u>
141	<input checked="" type="checkbox"/>	<u>Mycobacterium avium</u> <u>subsp. paratuberculosis</u> <u>str. k10</u>	4.8	4,830,681	Feb 5, 2004	<u>AE016958</u>	<u>mavi.seq</u>	<u>mavi.mne</u>
142	<input checked="" type="checkbox"/>	<u>Treponema denticola</u> <u>ATCC 35405</u>	2.8	2,843,741	Feb, 9, 2004	<u>AE017226</u>	<u>tden.seq</u>	<u>tden.mne</u>
143	<input checked="" type="checkbox"/>	<u>Wolbachia</u> <u>endosymbiont</u>	1.2	1,268,022	Feb, 13, 2004	<u>AE01722 6</u>	<u>wend.seq</u>	<u>wend.mne</u>
144	<input checked="" type="checkbox"/>	<u>Mycoplasma mycoides</u> <u>subsp. mycoides SC</u>	0.3	347,558	Feb, 13, 2004	<u>BX293980</u>	<u>mmyc.seq</u>	<u>mmyc.mne</u>
145	<input checked="" type="checkbox"/>	<u>Thermus thermophilus</u> <u>HB27</u>	1.8	1,895,237	Apr 6, 2004	<u>AE017221</u>	<u>tthe.seq</u>	<u>tthe.mne</u>

(*) The FASTA sequences are the collection of entries in GenBank for the genome of the corresponding species. It may be some overlap in the different entries. For an access to the entire sequence (in one entry) see : <ftp://ftp.ebi.ac.uk/pub/databases/genomes/Bacteria/> or <ftp://ftp.ncbi.nih.gov/genomes/Bacteria/>

Data on Microbial Genomes at INFOBIOGEN

- Incomplete genomes
- Genomes in FASTA format
- Other links for microorganism genomes
- DEAMBULUM (Prokaryota genomes)
- BLAST2 on incomplete genomes is also possible (as a tool) using SRS6
- EMGLib SRS Coding sequences of completed genomes
- EMGPep SRS Protein sequences of completed genomes

Others links

Exhibit D

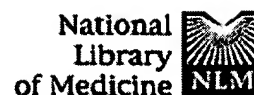
- **EMGLib** Enhanced Microbial Genomes Library - PBIL Lyon
- **MICADO** INRA - Jouy en Josas
- **COLIPAGE** Institut de Génétique - Orsay
- **Completed Genomes at the EBI**
- **Directory /genomes/Bacteria - EBI FTP**
- **Genome Centers and Databases - NCBI**
- **Complete Genomes - NCBI**
- **Microbial genomes - NCBI all formats**
- **Directory /genomes/Bacteria on NCBI FTP**

- **GOLD : Genomes OnLine Database (Nikos Kirpides)**
- **Complete genome papers**
- **Genome sequencing projects (Terry Gaasterland)**
- **TIGR Microbial Database**
- **MUMmer: The Whole Genome Alignment Tool - TIGR**
- **The Comprehensive Microbial Resource Home Page - TIGR**
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- **Completely Sequenced Genomes - Rockefeller**
- **SACSO: Systematic Analysis of Completely Sequenced Organisms**
- **DNA Structural Analysis of Complete Genomes and Chromosomes CBS - Denmark**
- **MBGD Microbial Genome Database for Comparative Analysis - Japan**
- **PEDANT - Genome analysis and annotation at MIPS**
- **HAMAP High quality Automated Microbial Annotation of Proteomes HAMAP Links**
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- **Life on Earth**

Comments and suggestions to: [dessen@infobiogen.fr]



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- Lancet. 2001 Apr 21;357(9264):1218-9.

ELSEVIER SCIENCE
FULL-TEXT ARTICLE**Whole genome sequencing of meticillin-resistant *Staphylococcus aureus*.**

Kuroda M, Ohta T, Uchiyama I, Baba T, Yuzawa H, Kobayashi I, Cui L, Oguchi A, Aoki K, Nagai Y, Lian J, Ito T, Kanamori M, Matsumaru H, Maruyama A, Murakami H, Hosoyama A, Mizutani-Ui Y, Takahashi NI, Sawano T, Inoue R, Kaito C, Sekimizu K, Hirakawa H, Kuhara S, Goto Yabuzaki J, Kanehisa M, Yamashita A, Oshima K, Furuya K, Yoshino C, Shiba T, Hattori M, Ogasawara N, Hayashi H, Hiramatsu K.

Hiramatsu, Department of Bacteriology, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, 113-8421, Tokyo, Japan.

BACKGROUND: *Staphylococcus aureus* is one of the major causes of community-acquired and hospital-acquired infections. It produces numerous including superantigens that cause unique disease entities such as toxic-shock syndrome and staphylococcal scarlet fever, and has acquired resistance to practically all antibiotics. Whole genome analysis is a necessary step towards future development of countermeasures against this organism. **METHODS:** genome sequences of two related *S. aureus* strains (N315 and Mu50) were determined by shot-gun random sequencing. N315 is a meticillin-resistant *S. aureus* (MRSA) strain isolated in 1982, and Mu50 is an MRSA strain with vancomycin resistance isolated in 1997. The open reading frames were identified by use of GAMBLER and GLIMMER programs, and annotation of each was with a BLAST homology search, motif analysis, and protein localisation prediction. **FINDINGS:** The *Staphylococcus* genome was composed of a complex mixture of genes, many of which seem to have been acquired by lateral gene transfer. Most of the antibiotic resistance genes were carried either by plasmids or by mobile genetic elements including a unique resistance island. Three classes of new pathogenicity islands were identified in the genome: a toxic-shock-syndrome toxin island family, exotoxin islands, and enterotoxin islands. In the latter two pathogenicity islands, clusters of exotoxin and enterotoxin genes were found closely linked with other gene clusters encoding putative pathogenic factors. The analysis also identified 70 candidates for new virulence factors.

INTERPRETATION: The remarkable ability of *S. aureus* to acquire useful genes

Exhibit E

from various organisms was revealed through the observation of genome complexity and evidence of lateral gene transfer. Repeated duplication of genes encoding superantigens explains why *S aureus* is capable of infecting human diverse genetic backgrounds, eliciting severe immune reactions. Investigation of many newly identified gene products, including the 70 putative virulence factors will greatly improve our understanding of the biology of staphylococci and the processes of infectious diseases caused by *S aureus*.

PMID: 11418146 [PubMed - indexed for MEDLINE]

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